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A population-based case-control study of the association between weather-related extreme heat events and neural tube defects

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Abstract

Background—Elevated body core temperature has been shown to have teratogenic effects in animal studies. Our study evaluated the association between weather-related extreme heat events (EHEs) in the summer season and neural tube defects (NTDs), and further investigated whether pregnant women with a high pre-gestational body mass index (BMI) have a greater risk of having a child with NTDs associated with exposure to EHE than women with a normal BMI.

Methods—We conducted a population-based case-control study among mothers of infants with NTDs and mothers of infants without major birth defects, who participated in the National Birth Defects Prevention Study and had at least one day of the third or fourth week post-conception

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Conflict of interest

The authors have no conflict of interest to declare.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, or the views or policies of the Environmental Protection Agency (EPA), or the views of the California Department of Public Health.

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during summer months. EHEs were defined using the 95th and the 90th percentiles of the daily maximum universal apparent temperature. Adjusted odds ratios and 95% confidence intervals were calculated using unconditional logistic regression models with Firth's penalized likelihood method while controlling for other known risk factors.

Results—Overall, we did not observe a significant association between EHEs and NTDs. At the climate region level, consistently elevated but not statistically significant estimates were observed for EHE95 in New York (Northeast), North Carolina and Georgia (Southeast), and Iowa (Upper Midwest). No effect modification by BMI was observed.

Conclusion—EHEs occurring during the relevant developmental window of embryogenesis do not appear to appreciably affect the risk of NTDs. Future studies should refine exposure assessment, and more completely account for maternal activities that may modify the effects of weather exposure.

Keywords

congenital malformations; neural tube defects; weather-related extreme heat

Introduction

Neural tube defects (NTDs) are central nervous system (CNS) malformations secondary to neural tube closure failure that occurs during early embryogenesis, between the third and fourth weeks postconception (Greene and Copp, 2014). The etiologies of NTDs are not fully understood, although research to date has identified maternal factors associated with variation in the prevalence of NTDs such as maternal obesity, age, parity, multiple gestations, diabetes, dietary factors, parental occupational exposure, and parental socio-economic status (SES)(Frey and Hauser, 2003; Shaw et al., 1996; Correa et al., 2008; Lupo et al., 2012).

Elevated body core temperature has been shown to have teratogenic effects. Several human studies that evaluated the association between elevated body temperature during the periconceptional period (Li et al., 2007; Lynberg et al., 1994; Shaw et al., 1998; Suarez et al., 2004; Shaw et al., 1999) or first trimester (Layde et al., 1980; Duong et al., 2011; Milunsky et al., 1992) and NTDs reported significantly increased risk of NTDs associated with maternal fever or febrile illness (Layde et al., 1980; Li et al., 2007; Lynberg et al., 1994; Shaw et al., 1998; Suarez et al., 2004), exposure to heat via hot tub (Duong et al., 2011; Milunsky et al., 1992), and use of heat devices (Suarez et al., 2004). In addition, in a meta-analysis on maternal hyperthermia and the risk of NTDs conducted by Moretti et al., the authors evaluated 15 studies (nine case-control; six prospective cohort studies) and observed an odds ratio (OR) = 1.93, 95% confidence interval (CI): 1.53, 2.42 (Moretti et al., 2005).

Despite evidence that heat exposure may be a risk factor for adverse pregnancy outcomes, pregnant women are not considered vulnerable to weather-related temperature extremes (Auger et al., 2017; Rylander et al., 2013; Strand et al., 2011). To our knowledge, there has been virtually no research conducted on the impact of weather-related extreme heat events

(EHEs) on NTDs. We identified only one article that evaluated the association between hyperthermia inducing activities such as walking, working, or running in the sun and NTDs, which reported no significant association (Suarez et al., 2004).

To help address this gap, we evaluated the association between EHEs in the summer season (June, July, August) and NTDs and assessed whether pregnant women with an elevated pre-gestational body mass index (BMI) are at higher risk of having a child with NTDs associated with exposure to weather-related extreme heat conditions than women with a normal BMI. Results of previous studies suggest that a high pre-gestational BMI is associated with increased risk of NTDs (McMahon et al., 2013; Shaw et al., 2000). In addition, obesity is associated with increased heat production and may interfere with normal thermoregulation (Savastano et al., 2009).

Material and methods

Study design and study population

We used a case-control design to examine the association between EHEs during the critical period of embryogenesis when the neural tube closure occurs, defined as weeks three and four of gestation (Detrait et al., 2005), and NTDs. Our study sample consisted of singleton NTD cases and non-malformed controls from the National Birth Defects Prevention Study (NBDPS) with estimated dates of delivery (EDD) from October 1, 1997 through December 31, 2007, and whose mothers resided in the study area at the time of delivery and had their residence geocoded. The NBDPS is a multi-site population-based case-control study that investigated genetic and environmental risk factors for over 30 major structural birth defects. Data were collected by study sites in ten states: Arkansas (AR), California (CA), Georgia (GA), Iowa (IA), Massachusetts (MA), New Jersey (NJ), New York (NY), North Carolina (NC), Texas (TX), and Utah (UT). Comprehensive methods for data collection have been previously described (Reefhuis et al., 2015).

For our study, eligible case deliveries included singleton live births, stillbirths, and elective terminations diagnosed with a NTD subtype: anencephaly and craniorachischisis, spina bifida, and encephalocele. Cases were identified from birth defect surveillance systems, and abstracted medical record information was reviewed by experienced clinical geneticists to ensure that each case met the specified diagnostic criteria (Rasmussen et al., 2003).

The control group consisted of singleton live-born infants without major birth defects who were randomly selected by month of birth from either hospital delivery records or electronic birth certificates. We excluded cases and controls whose mothers resided in NJ (residential address not geocoded); MA (due to delays in IRB approval); those at other sites whose mothers' residential address was not geocoded or was incorrectly geocoded; and those whose mothers reported being diagnosed with pre-gestational diabetes, due to the known teratogenic effect of hyperglycemia and increased risk of NTDs (Correa et al., 2008; Frey and Hauser, 2003; Lupo et al., 2012). Also, we excluded cases and controls whose mothers were not in the third or fourth week after conception during summer months. Figure 1 shows the exclusion criteria used for our study. The final analytic sample consisted of 326 NTD cases and 1,781 controls.

Mothers of case and control infants were interviewed in English or Spanish language using a one-hour computer assisted telephone interview (CATI), no earlier than six weeks after the infant's EDD, and no later than 24 months after EDD (Tinker et al., 2013). The information collected included demographics; maternal medical history; medication use; pregnancy history and complications; maternal diet; folic acid/multivitamin use; caffeine, tobacco, alcohol, and illicit drug use; parental occupations; residential history; and other behaviors and environmental exposures that occurred from three months before conception through birth. The NBDPS protocol was approved by the institutional review board at each site and at the Centers for Disease Control and Prevention (CDC), and participants provided informed consent.

Exposure assessment and definitions

Interviewers asked mothers to provide their addresses from three months before through the end of pregnancy. All addresses were geocoded at the CDC. If the mother reported multiple residences but the dates were missing, we conducted data imputation (on 16.4% of the study population) under the assumption the mechanism that led to missing dates was random, and we used the mean length-of-stay in one residence of mothers who reported complete residential history.

We obtained data on daily maximum temperature (Tmax) in degrees Fahrenheit (°F), dew point (°F), wind speed (in knots), and atmospheric pressure (in millibars) for each site from the National Center for Atmospheric Research (National Centers for Environmental Information, Climate Data Online). We calculated daily universal apparent maximum temperature (UATmax) using Steadman's formula (Steadman, 1984). We used UATmax as our exposure metric in the study because it combines temperature, humidity, and wind speed, and also captures the thermal stress and physiological discomfort of weather-related extreme heat more accurately than temperature alone (Madrigano et al., 2013; Van Zutphen et al., 2012).

We linked geocoded maternal residences to the closest weather monitoring station, which was used to assign the daily UATmax for each day of each participant's pregnancy. NTD cases and controls with at least one day of the critical period of embryogenesis occurring during the summer season were included in the analysis. We defined the summer season as the months of June, July, and August of each year.

We used two definitions of EHE: 1) at least two consecutive days with daily UATmax above the 95th percentile of the UATmax distribution for the season, year, and weather monitoring station (EHE95) (Anderson and Bell, 2011), and 2) at least three consecutive days with daily UATmax above the 90th percentile of the UATmax distribution for the season, year, and weather monitoring station (EHE90) (Van Zutphen et al., 2012). We created the following exposure indices: EHE (Yes/No), EHE frequency, and EHE duration. To account for the various impacts of high temperature in different geographical regions, as well as for the adaptability to extreme weather of people in different parts of the nation, we stratified our analyses by six climate regions: South (AR, TX), Southeast (NC, GA), Northeast (NY), Southwest (UT), West (CA), and Upper Midwest (IA) (National Centers for Environmental Information, U.S. Climate Regions).

Covariables

The following variables were derived from CATI interviews and evaluated as potential confounders: maternal age (≤19, 20–34, ≥35 years); race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other); maternal education level (<12, ≥12 years); parity (0, 1, ≥2 live births); prenatal care received (Yes/No); folic acid intake one month prior to and during the first month of the pregnancy (Yes/No); pre-gestational body mass index (BMI) (underweight, normal weight, overweight, obese); any reported fever one month prior to and during the first trimester (Yes/No); family history of an NTD (Yes/No); diuretic/laxative medication use one month prior through first trimester of the pregnancy (Yes/No), as it may interfere with thermoregulation during hot weather (Westaway et al., 2015); dietary caffeine consumption in the first trimester (>100 mg /≤100 mg /day); alcohol consumption in the first trimester (Yes/No); maternal smoking in the first trimester (Yes/No); and secondhand smoke exposure (SHS) in the first trimester (Yes/No). For a subset of the study cohort (n=1,481), we obtained the 2000 Standard Occupational Classification (SOC) System codes for occupations. Information obtained from the CATI interview was coded by a trained team of occupational epidemiologists and industrial hygienists. We classified participants with occupations that usually involve outdoor work and therefore potential exposure to high weather-related temperature as exposed, including farm work, construction work, and gardening.

Statistical analysis

We conducted univariable descriptive analysis for maternal sociodemographic characteristics and medical conditions that were evaluated as potential confounders. We used multivariable unconditional logistic regression models with Firth's penalized likelihood method to address issues of small sample size and/or quasi separation of data in various climate regions. We built reduced models through backward elimination and calculated adjusted odds ratios (aOR) overall and separately for each of the climate regions. The final models were adjusted for maternal age, maternal race/ethnicity, and BMI. We evaluated effect modification by maternal pre-gestational BMI dichotomized as < 25 kg/m^2, and ≥ 25 kg/m^2. We evaluated effect modification of BMI on the multiplicative scale as determined by the Likelihood Ratio test with an alpha of 0.05. To evaluate interaction on the additive scale, we computed the relative excess risk due to interaction (RERI) (Hosmer and Lemeshow, 1992).

We conducted sub-analyses to assess the association between EHEs and NTDs in various data subsets. Due to the distribution of variables and small sample size, we were unable to adjust for fever or diuretic/laxative medication use in our main analysis. To evaluate the potential residual confounding due to the lack of adjustment, we conducted sub-analyses among the following subgroups: participants who reported no fever during the first trimester of pregnancy; and participants who reported no diuretic medication use one month prior through first trimester of the pregnancy. To evaluate the impact of residential history imputation we evaluated the association between EHEs and NTDs among participants who reported complete residence history. To account for differences in termination rates across study centers, we conducted sub-analyses limited to live births. To evaluate the impact of distance from the monitoring station to maternal residence on the aOR estimates, we conducted analyses on study participants residing within geographical radii around the

weather station of 10 miles, 20 miles, and 30 miles, and compared the estimates to the aOR in each climate region. To evaluate the potential confounding effect of missing occupational exposure, we conducted logistic regression models on a subset of the study population that had information about their occupation. Lastly, we evaluated the association between EHEs and spina bifida and anencephaly, adjusting for maternal age, maternal race/ethnicity, and pre-gestational BMI. We used SAS 9.3 software for data management and logistic regression analysis.

Results

The study population included a total of 326 cases of NTDs (210 cases of spina bifida, 81 cases of anencephaly and craniorachischisis, and 35 cases of encephalocele) and 1,781 controls. Table 1 displays the distribution of various demographic characteristics and NTD risk factors by case status. Compared to control mothers, case mothers were more likely to report Hispanic ethnicity, less than 12 years of education, and fever during the first trimester of pregnancy. A slightly higher percentage of case mothers than control mothers were obese and reported no use of diuretics/laxatives.

Appendix Table 1 displays the mean values of the UATmax for the 95th (UATmax95%) and 90th (UATmax90%) percentiles by climate region. The overall UATmax95% difference between cases and controls was 0.97°F, while the overall UATmax90% difference between cases and controls was 0.96°F. The difference in temperature means between cases and controls was not statistically significant in any climate region. Appendix Table 2 shows the number and percent of cases and controls within each climate region who experienced an EHE in the summer season. A higher percentage of cases than controls experienced EHE95 in NC and GA (Southeast), NY (Northeast), and IA (Upper Midwest), while a higher percentage of cases than controls experienced EHE90 in UT (Southwest) and IA (Upper Midwest).

We did not observe any statistically significant associations between NTDs and EHE95 or EHE90, either by climate region or for the entire NBDPS study population (Table 2). Table 3 shows the aOR estimates of the association between EHE95 and EHE90 frequency and NTD occurrence by climate region, and overall for the NBDPS study population. No statistically significant association was observed for EHE95. We observed a statistically significant inverse association with NTDs for women who experienced one EHE90 occurrence compared to no EHE90 in CA (West); the risk among mothers in the same region who experienced two EHE90 was elevated but not significant.

EHE95 duration was not significantly associated with NTDs (Table 4). However, we did observe a borderline statistically inverse association between NTDs and EHE90 that were three days in duration for the entire study population overall, and, again, in CA(West). No other estimates for EHE90 duration were statistically significant. The highest estimates were observed in NY (Northeast) for both EHE95 and EHE90, but the confidence intervals were wide. In addition, the tests for trend for EHE frequency and duration were not statistically significant, with p-values ranging from 0.20 to 0.94.

We assessed effect modification by maternal pre-gestational BMI on both additive and multiplicative scales. Figure 2 shows the stratum-specific aOR estimates for the association between EHE95 and NTDs, and EHE90 and NTDs in the summer season. There was no evidence of effect modification by maternal pre-gestational BMI. Stratum-specific aOR estimates were not statistically significant, were close in value, and the confidence intervals overlapped. The RERI values did not show significant departure from additivity, −0.29 (−0.94, 0.36) for EHE95, and −0.17 (−0.75, 0.43) for EHE90. Appendix Table 3 displays the results of the association between EHE95/EHE90 and NTDs among selected subsets of the study sample. Sub-analysis results for both exposures were similar to those observed for the main analysis. We did not observe any overall or climate region-level associations between EHE95 (Yes/No) and EHE90 (Yes/No) and spina bifida or anencephaly.

Discussion

We conducted a population-based case-control study to assess the potential association between EHEs and NTDs in the summer season. We calculated estimates for five climate regions, as well as for the study population overall. We observed no statistically significant elevated risks between EHEs (yes/no) and NTDs overall or by each climate region. At the climate region level, consistently elevated but not statistically significant estimates were observed for EHE95 in New York (Northeast), North Carolina and Georgia (Southeast), and Iowa (Upper Midwest).

Our findings are seemingly consistent with those of Suarez et al., who observed an elevated but not significant estimate (OR = 1.4, 95% CI: 0.9,2.2) for the association between hyperthermia-inducing activities in hot environments such as “worked, walked, or ran in the sun” and NTDs in the state of TX (Suarez et al., 2004). Suarez et al. assessed the occurrence of the aforementioned activities throughout the first trimester regardless of season, and the authors adjusted for air conditioning usage at home or at work. NBDPS did not collect data on maternal physical activities during EHEs. Thus, our findings cannot be directly compared with the study by Suarez et al.

Further, we evaluated the association between the frequency and the duration of each category of EHE with NTDs. We hypothesized that repeated and/or sustained exposure to weather-related extreme heat increases the amount of thermal stress, thus potentially increasing the risk of NTDs associated with elevated body temperature. With respect to EHE frequency, similar to the study by Van Zutphen et al., we did not observe any statistically significant association for EHE90 frequency in NY (Northeast) (Van Zutphen et al., 2012). No literature to date has explored the relationship between the duration of EHEs and NTDs. In addition, we did not observe a dose-response relationship with the increase of frequency or duration of EHEs.

Somewhat surprisingly, we did observe a statistically significant inverse association between EHE90 frequency (one EHE *vs* no EHE) and NTDs in CA (West), and EHE90 duration (three days *vs* no EHE) and NTDs in CA (West) and overall in the NBDPS sample. These findings, however, may be due to chance. Out of the 82 statistical tests performed for the main analyses, we would expect four significant estimates at an alpha = 0.05. Also,

participating mothers from CA may be different than mothers from other sites; mothers from CA were younger, were more often of Hispanic ethnicity, had less education, reported less alcohol consumption and smoking, and reported less folic acid and diuretic/laxative intake than mothers from the other sites. An alternative explanation for the findings in CA may be that, of all the sites, California has the highest UATMax95% and UATMax90%, and that exposure to very high temperatures could result in early fetal loss and, therefore, in a lower probability of observed NTDs at the point such phenotypes would be detected and included in the NBDPS (Edwards et al., 2003).

We did not observe any interaction between EHEs and BMI and there is no literature to date to compare our findings. Lastly, we did not find any overall or climate region-level associations between EHE95 (Yes/No) and EHE90 (Yes/No) and spina bifida or anencephaly, specifically. In NY, Van Zutphen et al. evaluated the association between EHE90 and NTDs in the summer season and reported non-statistically significant estimates that ranged from OR = 0.21, 95% CI: 0.04, 1.03 for anencephaly to OR = 1.30, 95% CI: 0.82, 2.05 for spina bifida without anencephaly (Van Zutphen et al., 2012). Although our findings agree with those of VanZutphen et al. in that neither observed a statistically significant association between EHE90 and spina bifida and anencephaly, the difference between the estimates may be the result of the difference in definition of the vulnerability window (weeks 3–8 postconception) and the differences in exposure assessment (14 weather regions in New York State) (Van Zutphen et al., 2012).

In addition to the main analysis, we evaluated the association between EHEs and NTDs among participants who reported no diuretic medication use one month prior through first trimester of the pregnancy; participants who reported no fever during the first trimester of pregnancy; and participants who reported complete residence history. Also, we conducted sub-analyses among the live births to account for differences in termination rates across study centers. The estimates for both EHE90 and EHE95 were similar to those of the main analysis.

Teratogenic mechanism of hyperthermia

The teratogenicity of maternal hyperthermia, due either to fever or environmental heat, has been reported in animal models (Graham, Jr. et al., 1998; Smith et al., 1978). It has been shown that the effects of hyperthermia depend on the timing of exposure and dose of heat, and that the central nervous system is particularly sensitive (Graham, Jr. et al., 1998). Several pathogenic mechanisms responsible for the teratogenic effect of heat have been described in the literature. Elevated body core temperature could result in mitotic inhibition and delay in cellular proliferation; protein denaturation and cell death; alteration in cell membrane and intracellular structures; microvascular disruptions and placental infarction; and enzyme inhibition (Edwards, 2006; Graham, Jr. et al., 1998). While the specific mechanism has not been fully articulated, it is clear that the window of vulnerability is quite small and that the mechanism involves disruption of a crucial step in fetal neurodevelopment. One explanation for the lack of association observed in our study may be that the core body temperature of mothers who experienced EHEs did not increase at a level that causes initiation of the pathogenic mechanisms.

Study strengths

To our knowledge, this study is among the first to evaluate the association between EHEs and the occurrence of NTDs. We conducted a large population-based case-control study in a geographically and racially diverse population over a ten-year time period. Maternal residential history collected via a CATI was used to conduct an objective assessment of exposure(s) during the vulnerable time window in fetal development. Centralized geocoding increased the consistency of the data across the NBDPS participating centers and improved the quality control of the geocoded data. The response rate for the time period between October 1, 1997 and December 31, 2007 was 68.5% for cases and 64.9% for controls, therefore decreasing to some extent the potential for self-selection bias. With respect to exposure definition, UATmax was used to define EHEs to better characterize the thermal stress experienced by the human body. We evaluated the impact of multiple exposure indicators to capture the potential effect of intensity and duration of the EHEs. Potential acclimatization was accounted for by using relative measure of weather-related extreme heat based on regional distribution of UATmax. NTDs are congenital malformations relatively easy to detect and diagnose at birth. To identify and classify the various subtypes of NTDs, case ascertainment was done in a systematic fashion by trained geneticists using standardized diagnostic criteria.

Study limitations

NTD occurrence may impact pregnancy outcomes as an NTD-affected pregnancy may end in fetal death or elective termination. To minimize the potential of ascertainment bias, NBDPS collected information on live births (all centers), fetal deaths of 20 weeks or greater gestation (six centers), and elective terminations (five centers). In addition, to account for differences in termination rates across study centers, we evaluated the association between EHEs and NTDs among the live births and found similar results. With respect to control selection, in a study that evaluated the representativeness of controls in the NBDPS, the authors concluded that control participants were representative of their source population (Cogswell et al., 2009).

Since exposure assessment was based on temperature measured at airport weather stations and not at an individual level, we lowered to some extent the potential of exposure misclassification by linking the maternal residence with the closest weather station. The mean distance between the maternal residence and the closest weather monitoring station varied across the climate regions, with study subjects from NY residing the closest (10.2 miles for cases and 10.6 for controls) and study subjects from the Southeast residing the farthest (39.2 miles for cases and 34.9 for controls); however, the differences in mean distance from the residence to the weather monitoring station were not significant by case/ control status. We evaluated the impact of distance from the monitoring station on the aOR estimates by conducting analyses on study participants residing within geographical radii of 10 miles, 20 miles, and 30 miles around the weather monitoring stations, and compared the estimates to the overall aOR for each climate region.

To evaluate the potential residual confounding due to occupational exposure to heat, we conducted analysis on a subset of study participants that had their occupation coded by a

team of occupational epidemiologists and industrial hygienists (208 NTD cases and 1,210 controls). The estimates adjusted for occupational exposure to heat were similar to the estimates in the primary analysis. We cannot rule out residual confounding as factors such as indoor temperature, behaviors that may alter the exposure to heat (e.g., hydration, air conditioner use, use of hot tub/bath, time spent outdoors), and use of folate antagonist medication were not controlled for in the analysis. Due to the small number of exposed cases and controls, we did not have good statistical power to detect associations within climate regions. In addition, some of our significant estimates may be due to chance, as we conducted many statistical tests.

In conclusion, weather-related extreme heat events occurring during the relevant developmental window of embryogenesis did not seem to appreciably affect the risk of NTDs. No modifying effect was observed for increased BMI. Future studies should refine exposure assessment by measuring body temperature using personal monitors, and more completely account for maternal activities that may modify the effects of weather exposure.

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Appendix

Appendix Table 1

Mean value of 95th and 90th percentiles of the universal apparent maximum temperature in the summer season, NBDPS, 1997–2007

Climate region	Weather Monitoring Stations	Mean UATmax95% (°F)		P value*	Mean UATmax90% (°F)		P value*
	N	Cases	Controls		Cases	Controls	
South (AR, TX)	61	99.92	100.17	0.76	98.29	98.57	0.74
Southeast (NC, GA)	25	98.06	97.08	0.22	96.23	95.27	0.26
Northeast (NY)	16	88.46	87.80	0.73	85.84	84.56	0.53
Southwest (UT)	12	95.11	94.37	0.63	92.54	91.76	0.65
West (CA)	16	100.94	100.74	0.85	97.88	97.93	0.96
Upper Midwest (IA)	—**	91.90	91.86	0.98	89.46	89.12	0.79
Overall NBDPS	130	97.28	96.31	0.06	94.97	94.01	0.09

*Two-sample t-test; UATmax95% = 95th percentile of the mean daily universal apparent maximum temperature distribution in the summer season; UATmax90% = 90th percentile of the mean daily universal apparent maximum temperature distribution in the summer season; °F = degrees Fahrenheit; AR = Arkansas; TX = Texas; NC = North Carolina; GA = Georgia; NY = New York; UT = Utah; CA = California; IA = Iowa; NBDPS = National Birth Defects Prevention Study

**Due to IRB restrictions on sharing geocoded information in IA, the number of weather monitoring stations could not be assessed.

Appendix Table 2

NTD cases and controls who experienced extreme heat events by climate region, NBDPS, 1997–2007

	EHE95		EHE90	
Climate Region	**Cases N (%)**	**Controls N (%)**	**Cases N (%)**	**Controls N (%)**
South (AR, TX)	18 (23.68)	141 (30.79)	17 (22.37)	151 (32.97)
Southeast (NC, GA)	18 (27.69)	103 (26.14)	14 (21.54)	104 (26.40)
Northeast (NY)	6 (26.09)	40 (18.78)	4 (17.39)	42 (19.72)
Southwest (UT)	13 (41.94)	70 (41.67)	14 (45.16)	73 (43.45)
West (CA)	19 (23.75)	101 (35.82)	24 (30.00)	117 (41.49)
Upper Midwest (IA)	18 (35.29)	83 (31.20)	18 (35.29)	78 (29.32)
Overall NBDPS	92 (28.22)	538 (30.21)	91 (27.91)	565 (31.72)

EHE95 = extreme heat event defined as at least two consecutive days with daily universal apparent maximum temperature above the 95th percentile of the universal apparent maximum temperature distribution for the summer season and for climate region; EHE90 = extreme heat event defined as at least three consecutive days with daily universal apparent maximum temperature above the 90th percentile of the universal apparent maximum temperature distribution for the summer season and for climate region; NTDs = neural tube defects; AR = Arkansas; TX = Texas; NC = North Carolina; GA = Georgia; NY = New York; UT = Utah; CA = California; IA = Iowa, NBDPS = National Birth Defects Prevention Study

Appendix Table 3

Adjusted odds ratio estimates of the association between EHE95/EHE90 and NTDs among selected subgroups, NBDPS, 1997–2007

Subsets of data	**EHE95 aOR (95% CI)** *	**EHE90 aOR (95% CI)** *
No diuretic medication use in the first trimester	0.90 (0.68, 1.19)	0.81 (0.61, 1.08)
No fever in the first trimester	0.94 (0.71, 1.25)	0.75 (0.56, 1.01)
Complete residence history	0.99 (0.74, 1.32)	0.90 (0.67, 1.21)
Live births	0.92 (0.67, 1.24)	0.79 (0.58, 1.08)
Geographic radius around weather station		
10 miles	0.89 (0.61, 1.32)	0.84 (0.57, 1.24)
20 miles	0.95 (0.68, 1.31)	0.79 (0.57, 1.10)
30 miles	0.92 (0.68, 1.25)	0.78 (0.57, 1.06)
Occupation with potential exposure to elevated environmental temperature	0.98 (0.71, 1.36)	0.93 (0.67, 1.28)
Spina bifida (overall NBDPS)	0.97 (0.70, 1.34)	0.82 (0.59, 1.13)
South (AR, TX)	0.85 (0.46, 1.59)	0.74 (0.39, 1.38)
Southeast (NC, GA)	0.97 (0.45, 2.08)	0.65 (0.29, 1.49)
Northeast (NY)	1.32 (0.44, 3.92)	0.66 (0.19, 2.31)
Southwest (UT)	1.13 (0.47, 2.69)	1.01 (0.42, 2.45)
West (CA)	0.51 (0.23, 1.16)	0.53 (0.25, 1.12)
Upper Midwest (IA)	1.35 (0.62, 2.94)	1.23 (0.56, 2.72)
Anencephaly (overall NBDPS)	1.00 (0.62, 1.62)	0.86 (0.53, 1.40)

Subsets of data	EHE95 aOR (95% CI) *	EHE90 aOR (95% CI) *
South (AR, TX)	0.68 (0.22, 2.06)	0.35 (0.10, 1.24)
Southeast (NC, GA)	1.88 (0.75, 4.67)	0.82 (0.29, 2.29)
Northeast (NY)	6.64 (0.67, 19.88)	3.64 (0.67, 19.85)
Southwest (UT)	0.53 (0.10, 2.91)	1.65 (0.33, 8.17)
West (CA)	0.93 (0.39, 2.22)	0.86 (0.37, 1.98)
Upper Midwest (IA)	0.80 (0.27, 2.35)	1.26 (0.44, 3.58)

*Adjusted for maternal age, maternal race/ethnicity and maternal body mass index (BMI)

EHE95 = extreme heat event defined as at least two consecutive days with daily universal apparent maximum temperature above the 95th percentile of the universal apparent maximum temperature distribution for the summer season and for climate region; EHE90 = extreme heat event defined as at least three consecutive days with daily universal apparent maximum temperature above the 90th percentile of the universal apparent maximum temperature distribution for the summer season and for climate region; NTDs = neural tube defects; NBDPS = National Birth Defects Prevention Study; aOR = adjusted odds ratio; CI = confidence interval; AR = Arkansas; TX = Texas; NC = North Carolina; GA = Georgia; NY = New York; UT = Utah; CA = California; IA = Iowa

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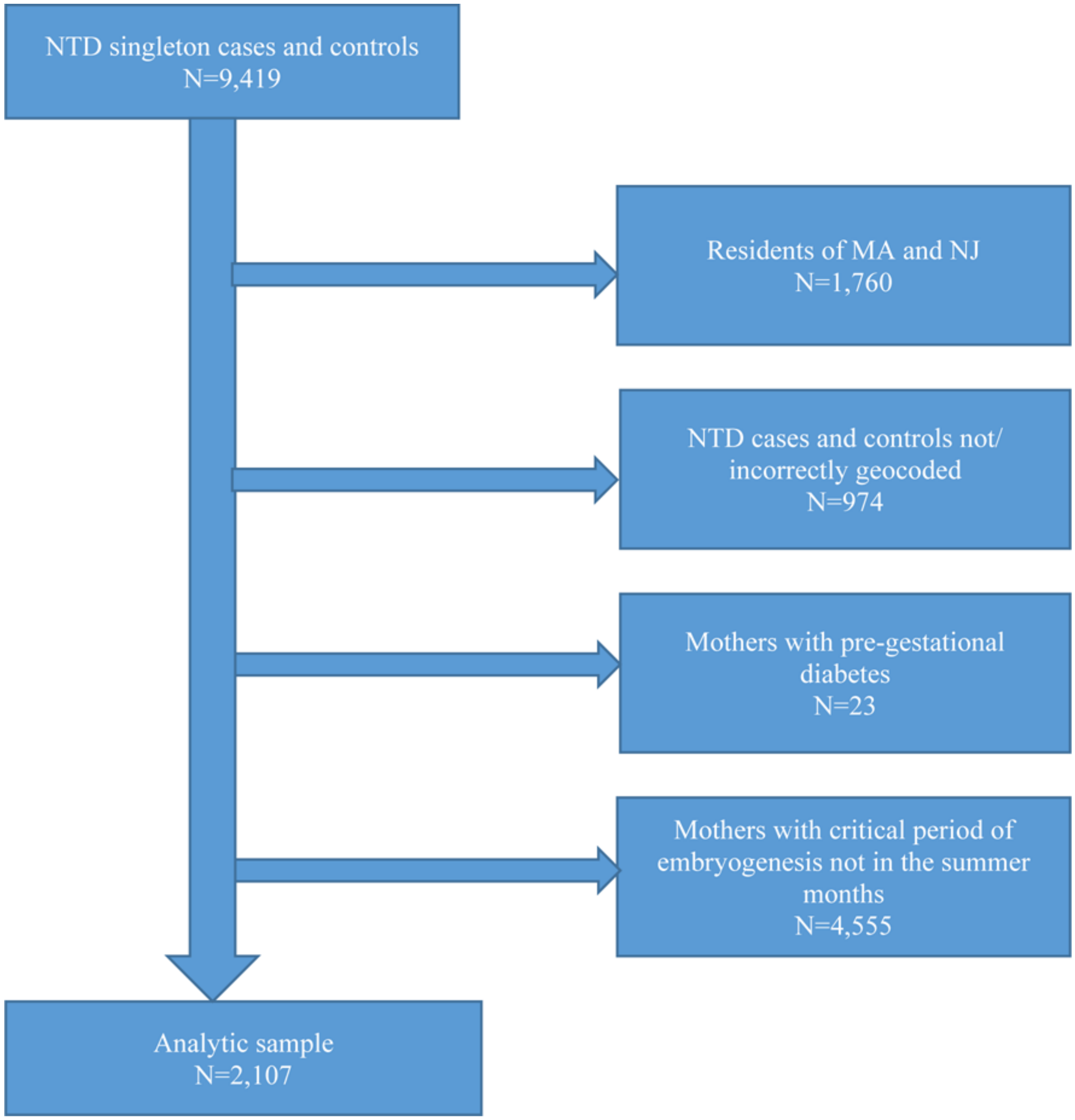

Figure 1.

Exclusion criteria for neural tube defect cases and controls sample, National Birth Defects Prevention Study, 1997–2007

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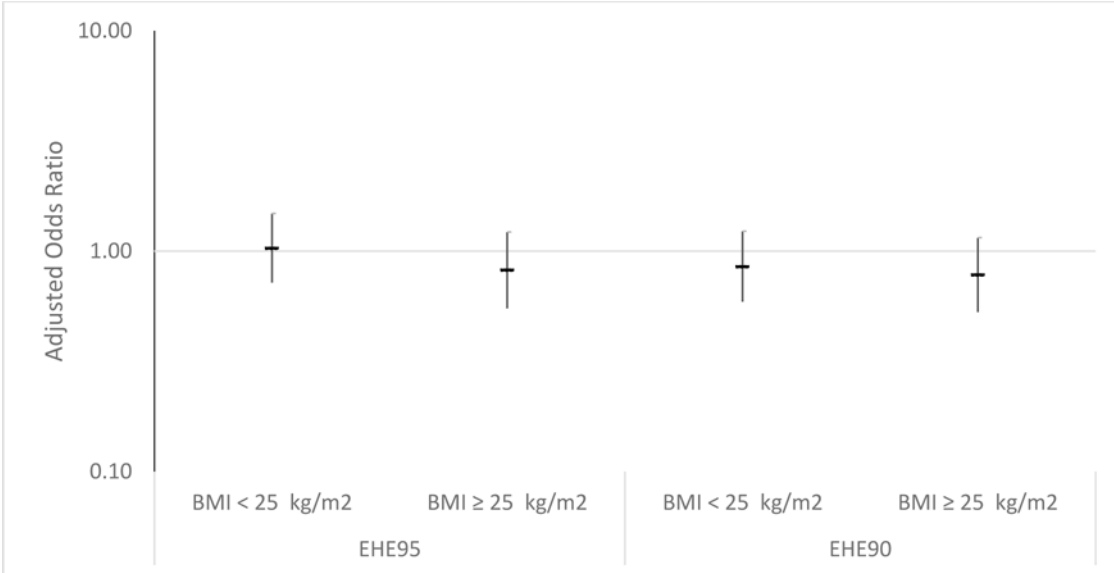

Figure 2.
Adjusted odds ratios of the association between extreme heat events (EHE) and neural tube defects stratified by body mass index (BMI)

Table 1

Distribution of socio-demographic characteristics between NTD cases and controls, NBDPS, 1997–2007

Maternal characteristics	Cases (N=326)		Controls (N=1,781)		χ^{2*}
	N	%	N	%	
Maternal age					
≤19 years	45	13.80	214	12.02	0.22
20–34 years	231	70.86	1,342	75.35	
≥35 years	50	15.34	225	12.63	
Maternal race					
White non-Hispanic	172	52.76	989	55.53	0.05
Black non-Hispanic	29	8.90	229	12.86	
Hispanic	101	30.98	448	25.15	
Other/Mixed	24	7.36	114	6.40	
Maternal education					
<12 years	168	51.53	752	42.22	0.0023
≥12 years	155	47.55	1,003	56.32	
Parity					
0	108	33.13	678	38.07	0.18
1	114	34.97	606	34.03	
≥2	104	31.90	497	27.91	
Prenatal care					
Yes	320	98.16	1,759	98.76	0.28
No	6	1.84	20	1.12	
Folic acid use first month					
Yes	160	49.08	852	47.84	0.68
No	166	50.92	929	52.16	
Body mass index					
Underweight (BMI < 18.5)	16	4.91	87	4.88	0.11
Normal (18.5 ≤ BMI < 25)	146	44.79	923	51.82	
Overweight (25 ≤ BMI < 30)	77	23.62	382	21.45	
Obese (BMI≥ 30)	70	21.47	307	17.24	

Maternal characteristics	Cases (N=326)		Controls (N=1,781)		χ^{2*}
	N	%	N	%	
Fever first trimester					
Yes	34	10.43	107	6.01	0.003
No	292	89.57	1,674	93.99	
Family history of NTDs **					
Yes	4	1.23	7	0.39	0.05
No	322	98.77	1,774	99.61	
Diuretics/laxatives first trimester					
Yes	31	9.51	232	13.03	0.08
No	295	90.49	1,547	86.86	
Caffeine first trimester					
>100 mg	141	43.25	736	41.33	0.52
≤100 mg	185	56.75	1,045	58.67	
Alcohol consumption first trimester					
Yes	112	34.36	572	32.12	0.49
No	212	65.03	1,182	66.37	
Maternal smoking first trimester					
Yes	65	19.94	303	17.01	0.21
No	259	79.45	1,460	81.98	
Secondhand smoke first trimester					
Yes	90	27.61	421	23.64	0.12
No	232	71.17	1,338	75.13	
Climate region					
South (AR, TX)	76	23.31	458	25.72	0.002
Southeast (NC, GA)	65	19.94	394	22.12	
Northeast (NY)	23	7.06	213	11.96	
Southwest (UT)	31	9.51	168	9.43	
West (CA)	80	24.54	282	15.83	
Upper Midwest (IA)	51	15.64	266	14.94	
Imputed maternal residence dates					0.08
Yes	64	19.63	281	15.78	

Maternal characteristics	Cases (N=326)		Controls (N=1,781)		χ^{2*}
	N	%	N	%	
No	262	80.37	1,500	84.22	

* Chi-square test of equal proportions;

** Fisher's exact test; the total percentage may not add to 100 because the counts on variables with missing values are not shown.

NTD = neural tube defects; NBDPS = National Birth Defects Prevention Study; BMI = body mass index; AR = Arkansas; TX = Texas; NC = North Carolina; GA = Georgia; NY = New York; UT = Utah; CA = California; IA = Iowa

Table 2

Adjusted odds ratio estimates of the association between EHE95(Yes/No)/EHE90(Yes/No) and NTDs by climate region, NBDPS, 1997–2007

Climate Region	Cases/Controls who experienced EHE95	EHE95 aOR (95% CI) *	Cases/Controls who experienced EHE90	EHE90 aOR (95% CI) *
	n		n	
South (AR, TX)	18/141	0.74 (0.42, 1.29)	17/151	0.62 (0.35, 1.10)
Southeast (NC, GA)	18/103	1.13 (0.63, 2.02)	14/104	0.78 (0.42, 1.46)
Northeast (NY)	6/40	1.32 (0.48, 3.63)	4/42	0.73 (0.23, 2.28)
Southwest (UT)	13/70	0.97 (0.44, 2.15)	14/73	0.99 (0.44, 2.21)
West (CA)	19/101	0.57 (0.31, 1.04)	24/117	0.56 (0.31, 1.00)
Upper Midwest (IA)	18/83	1.21 (0.63, 2.32)	18/78	1.29 (0.67, 2.49)
Overall NBDPS	92/538	0.93 (0.71, 1.21)	91/565	0.82 (0.62, 1.07)

*Adjusted for maternal age, maternal race/ethnicity, and maternal body mass index (BMI)

EHE95 = extreme heat event defined as at least two consecutive days with daily universal apparent maximum temperature above the 95th percentile of the universal apparent maximum temperature distribution for the summer season and for climate region; EHE90 = extreme heat event defined as at least three consecutive days with daily universal apparent maximum temperature above the 90th percentile of the universal apparent maximum temperature distribution for the summer season and for climate region; aOR = adjusted odds ratio; CI = confidence interval; AR = Arkansas; TX = Texas; NC = North Carolina; GA = Georgia; NY = New York; UT = Utah; CA = California; IA = Iowa; NBDPS = National Birth Defects Prevention Study

Table 3

Adjusted odds ratio estimates of the association between frequency of EHE95/EHE90 and NTDs by climate region, NBDPS, 1997–2007

	South (AR, TX)	Southeast (NC, GA)	Northeast (NY)	Southwest (UT)	West (CA)	Upper Midwest (IA)	Overall NBDPS
	aOR (95% CI) *	**aOR (95% CI) ***	**aOR (95% CI) ***	**aOR (95% CI) ***	**aOR (95% CI) ***	**aOR (95% CI) ***	**aOR (95% CI) ***
EHE95							
1 EHE vs 0	0.71 (0.40, 1.28)	1.10 (0.59, 2.05)	1.17 (0.41, 3.36)	1.06 (0.47, 2.39)	0.56 (0.30, 1.03)	1.38 (0.71, 2.67)	0.93 (0.70, 1.22)
2 EHEs vs 0	1.20 (0.27, 5.28)	1.47 (0.42, 5.09)	—	0.66 (0.10, 4.55)	1.35 (0.11, 16.14)	0.23 (0.01, 5.08)	0.99 (0.46, 2.10)
EHE90							
1 EHE vs 0	0.67 (0.38, 1.19)	0.89 (0.47, 1.68)	0.73 (0.23, 2.28)	0.96 (0.39, 2.36)	**0.51 (0.28, 0.93)**	1.45 (0.73, 2.87)	0.82 (0.62, 1.09)
2 EHEs vs 0	0.22 (0.01, 4.07)	0.21 (0.01, 3.97)	—	1.12 (0.35, 3.56)	1.52 (0.38, 6.14)	0.75 (0.16, 3.51)	0.80 (0.41, 1.57)

* Adjusted for maternal age, maternal race/ethnicity, and maternal body mass index (BMI)

EHE95 = extreme heat event defined as at least two consecutive days with daily universal apparent maximum temperature above the 95th percentile of the universal apparent maximum temperature distribution for the summer season and for climate region; EHE90 = extreme heat event defined as at least three consecutive days with daily universal apparent maximum temperature above the 90th percentile of the universal apparent maximum temperature distribution for the summer season and for climate region; NTDs = neural tube defects; aOR = adjusted odds ratio; CI = confidence interval; AR = Arkansas; TX = Texas; NC = North Carolina; GA = Georgia; NY = New York; UT = Utah; CA = California; IA = Iowa; NBDPS = National Birth Defects Prevention Study

Table 4

Adjusted odds ratio estimates of the association between duration of EHE95/EHE90 and NTDs by climate region, NBDPS, 1997–2007

	South (AR, TX) aOR (95% CI) *	Southeast (NC, GA) aOR (95% CI) *	Northeast (NY) aOR (95% CI) *	Southwest (UT) aOR (95% CI) *	West (CA) aOR (95% CI) *	Upper Midwest (IA) aOR (95% CI) *	Overall NBDPS aOR (95% CI) *
EHE95							
2 days vs 0	0.73 (0.37, 1.43)	1.15 (0.59, 2.23)	0.83 (0.24, 3.94)	0.85 (0.33, 2.18)	0.50 (0.21, 1.20)	1.02 (0.46, 2.27)	0.81 (0.58, 1.13)
3 days vs 0	0.92 (0.35, 2.41)	1.58 (0.52, 4.82)	3.28 (0.56, 19.13)	1.43 (0.40, 5.17)	0.56 (0.23, 1.39)	1.35 (0.43, 4.20)	1.16 (0.74, 1.82)
4 days vs 0	0.71 (0.18, 2.83)	0.76 (0.13, 4.44)	6.95 (0.57, 84.68)	1.21 (0.26, 5.67)	0.84 (0.29, 2.41)	2.25 (0.66, 7.70)	1.14 (0.64, 2.02)
EHE90							
3 days vs 0	0.57 (0.26, 1.28)	0.70 (0.31, 1.60)	0.60 (0.15, 2.44)	1.42 (0.45, 4.49)	**0.33 (0.12, 0.94)**	1.12 (0.46, 2.77)	**0.66 (0.45, 0.98)**
4 days vs 0	0.26 (0.05, 1.37)	0.54 (0.14, 2.04)	2.44 (0.38, 15.92)	1.28 (0.25, 6.48)	0.53 (0.21, 1.34)	1.52 (0.51, 4.48)	0.77 (0.46, 1.28)
5 days vs 0	0.99 (0.46, 2.11)	1.56 (0.57, 4.29)	0.50 (0.02, 12.16)	0.84 (0.32, 2.19)	0.89 (0.42, 1.91)	1.54 (0.56, 4.22)	1.09 (0.74, 1.59)

* Adjusted for maternal age, maternal race/ethnicity, and maternal body mass index (BMI)

EHE95 = extreme heat event defined as at least two consecutive days with daily universal apparent maximum temperature above the 95th percentile of the universal apparent maximum temperature distribution for the summer season and for climate region; EHE90 = extreme heat event defined as at least three consecutive days with daily universal apparent maximum temperature above the 90th percentile of the universal apparent maximum temperature distribution for the summer season and for climate region; NTDs = neural tube defects; aOR = adjusted odds ratio; CI = confidence interval; AR = Arkansas; TX = Texas; NC = North Carolina; GA = Georgia; NY = New York; UT = Utah; CA = California; IA = Iowa; NBDPS = National Birth Defects Prevention Study